(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 947 199 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
06.10.1999 Bulletin 1999/40

(51) Int. Cl.[6]: A61K 33/26, A61K 9/50

(21) Application number: 99301390.3

(22) Date of filing: 25.02.1999

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: 27.02.1998 CA 2230801

(71) Applicant: Zlotkin, Stanley H.
Toronto, Ontario M5R 1L9 (CA)

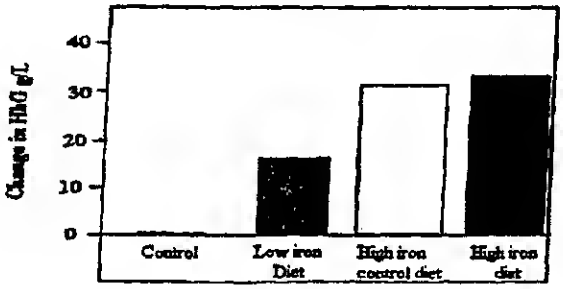
(72) Inventor: Zlotkin, Stanley H.
Toronto, Ontario M5R 1L9 (CA)

(74) Representative:
Jones, Helen Marjorie Meredith
Gill Jennings & Every,
Broadgate House,
7 Eldon Street
London EC2M 7LH (GB)

(54) Composition comprising micro-encapsulated iron

(57) A composition useful in the prevention of iron deficiency anemia is provided. The composition comprises micro-encapsulated iron granules in combination with a lipid-based excipient. The composition may additionally contain other micronutrients including ascorbic acid, zinc, vitamin A and iodine. The composition is particularly useful for the prevention of iron deficiency anemia in infants between the ages of 6 and 24 months of age since it can readily be admixed with the semi-solid foods this age group consumes.

Figure 1



EP 0 947 199 A1

Description

Field of the Invention

[0001] The present invention relates to micronutrient supplements. More particularly, the present invention relates to micronutrient supplements comprising iron which are especially useful for administration to infants.

Background of the Invention

[0002] Micronutrient malnutrition may be defined as the insufficient dietary consumption of nutrients such as vitamin A, iron and iodine. It is a significent problem affecting more than 2 billion people worldwide, particularly women and children living in poverty. Iron deficiency is the most common nutritional problem in the world, affecting two thirds of children in most developing nations. Anemia resulting from iron deficiency in young children has become very common since the level of bioavailable iron in a typical infant's diet is low while their rapid growth requires a much higher level of iron. The consequences of iron deficiency anemia (IDA) are very serious as it is associated with impaired cognitive and psychomotor development, reduced growth and decreased resistance to infection.

[0003] The age group at most risk is infants 6 to 24 months of age. Infants up to 6 months of ege are protected from deficiency by iron stores present at birth and iron obtained from breast milk. Children 2 years of ege and older obtain bioavailable iron from a diversifying diet. For infants between the ages of 6 to 24 months, however, iron obtained from breast milk cannot sufficiently meet the needs of rapid growth, while the solid food diet of this age group is not diversified enough to provide the required iron.

[0004] Micronutrient malnutrition, end more particularly iron deficiency, can be prevented, or et least controlled, by diet diversification, food fortification and nutrient supplementation. However, these solutions cannot readily be implemented in developing countries. For example, the ability of those in developing countries to diversify their diet is dictated not only by the availability of foods with a high nutrient content, but more importantly by the cost of such foods. Iron-fortified foods are, of course, an appropriate, effective means to prevent anemia; however, the cost of these foods is prohibitive to most families living in developing countries. The solution appears to lie in the remaining alternative, iron supplements, assuming that suitable cost-effective supplements can be developed for administration to infants and young children.

[0005] Currently, iron supplements are available for administration to intants and young children in the form of a concentrated solution or syrup due to the fact that they cannot swallow tablets or pills. However, in comparison to the use of tablets or pills, use of these formulations is associated with significant disedventeges. At the outset, shipping and storage of such iron-containing formulations is more costly and these formulations have a shorter shelf-life than comparable tablets or pills. Solution formulations are also more complicated to dispense and, as a result, there exists e higher liklihood of dispensing incorrect dosages. Further, there is poor compliance with liquid formulations because of their unpleasant metallic taste. Finally, administration of iron in solution can cause stains on teeth, a disadvantage which is reversible but undesirable in the interim.

[0006] There is a need, thus, to provide a cost-effective iron supplement suitable for administration to infants and young children which is useful to prevent iron deficiency anemia.

Summary of the Invention

[0007] The present invention provides a composition supplemented with iron which is particularly suitable for administration to infants, and more particularly, suitable for administration to infants and young children, i.e. children under 2 years of age.

[0008] Accordingly, in one aspect, the present invention provides a composition comprising micro-encapsulated iron granules in combination with a pharmaceutically acceptable lipid-based excipient.

[0009] In another aspect of the present invention, there is provided e method for preventing iron deficiency anemie in a mammal comprising the steps of adding a therapeutically effective amount of a composition comprising micro-encapsulated iron granules and a pharmaceutically acceptable lipid-based excipient to food and administering the food to said mammal.

[0010] In another aspect of the present invention, there is provided an article of manufacture comprising packaging materiel and a pharmaceutical composition contained within said packaging material, wherein said pharmaceutical composition is therapeutically effective to prevent iron deficiency anemia, and wherein the packaging materiat comprises a label which indicates that the composition comprises iron and that iron ingestion is effective to prevent iron deficiency anemia, said composition comprising a therapeutically effective amount of micro-encapsulated iron granules in combination with a pharmaceutically acceptable lipid-based excipient.

[0011] In yet another aspect of the present invention, there is provided an article of manufacture comprising packag-

ing material and a pharmaceutical composition contained within said packaging material, wherein said pharmaceutical composition is therapeutically effective to prevent iron deficiency anemie, and wherein the peckaging materiel comprises a label which indicates that the composition can be used to prevent iron deficiency anemia, said composition comprising a therapeutically effective amount of micro-encapsulated iron granules in combination with a pharmaceutically acceptable lipid-based excipient.

[0012] The present composition advantageously provides iron in e form which is readily administrable on addition to food, requiring no further preparation prior to administration. When added to food, the composition does not adversely affect the taste or appearance of food because it is encapsulated, thereby preventing any teaching that might otherwise occur. Moreover, the provision of micro-encapsulated iron in a lipid-based excipient makes the present composition useful for administretion to infants, particularly between the ages of 6-24 months, an age group which is especially vulnerable to iron deficiency. In this regard, the composition can be added directly to infant foods, including cereals, purees, formula end milk.

Brief Description of the Drawings

[0013]

FIGURE 1 is a bar graph illustrating the effect of various iron-containing compositions on hemoglobin response in rats.

Detailed Description of the Invention

[0014] The present invention provides a composition useful to prevent iron deficiency anemia comprising micro-encapsulated iron granules in combination with e pharmaceutically ecceptable lipid-based excipient. The term "prevent" as it is used herein with respect to the capacity of the present composition to affect the onset of iron deficiency anemia refers not only to prevention of the disease but may also refer to prevention of one or more of the adverse effects associeted with anemia.

[0015] The term "lipid-based", es it Is used herein with respect to the excipient, is meant to refer to excipients which are lipids, or which comprise a lipid component. Lipid-based excipients will combine with the micro-encapsulated iron granules of the present composition in a chemically stable manner in which no adverse interaction occurs such as undesirable aesthetic changes or undesirable changes to the taste of the product. Moreover, lipid-based excipients conveniently ellow combinetion of the composition with toods, the means by which it is administered.

[0016] The micro-encapsulated iron granules of the present composition may comprise any bioavailable solid form of iron including iron salts such as ferrous sulphate, ferrous fumarate, ferrous succinate, ferrous gluconate, ferric pyrophosphate, ferric saccharate, ferric orthophosphate or any other compound capable of providing iron with an appropriate bioavailability. Bioavailability can be determined using the standard "hemoglobin-repletion" method described in detail by Fritz et al. in the Journel of tha Association of Official Analytical Chemists (AOAC), 1974, 57:513-517 and by Williams in the Official methods of analysis of the AOAC, 14th edition, Arlington VA, AOAC, 1984, p.880-881. This method generally involves feeding anemic rats with a test iron compound and comparing their iron uptake with the iron uptake of anemic rats fed a reference compound determined to have a relative iron bioavailability of 100%.

[0017] The selected iron compound is formed into granules using techniques and machinery well-known to those of skill in the ert. For use in the present composition, granules are prepared heving e diemeter of no more than about 850 microns. Granules of this size renge can be obtained, for example, using a U.S. No. 20 sieve. The granulated iron compound is provided as a fine free flowing powder.

[0018] Once formed into granules of a desired size, the iron compound is coated or encapsulated with an inert substance that will not interfere with the uptake of the iron compound. The coating functions to sustain the release of the iron, effectively masking the characteristic unpleasant taste of the iron compound, preventing discoloration of the foods to which it is edded thereby providing e form of iron that can reedily be edded to foods. The coating elso prevents the undesirable interaction between nutrients in the foods to which it is added as well as additional nutrients thaf may be added to the composition itself. The inert coating may be selected from a number of suitable substances including, but not limited to, mono- or di-glycerides, ethyl cellulose, hydrogenated soybean oil, acacia gum and mixtures thereof.

[0019] The encapsulated granulated iron compound is admixed with a pharmaceutically acceptable lipid-based excipient. The term "pharmaceutically acceptable" refers to an excipient eccepteble for use in the phermaceuticel end veterinary arts, which Is not toxic or otherwise unacceptable. Examples of suitable lipid-based excipients include mono-, di- and tri-glycerides, especially naturally extracted unsaturated edible oils in hydrogenated form (such as vegetable oil, castor oil, cottonseed oil, corn oil, canola oil, rapeseed oil, peanut oil, sesame seed oil, coconut oil and mixtures thereof).

[0020] The present composition mey be supplemented with edditionel micronutrients. Such additional micronutrients

may function to enhance the absorption of iron on administration. In a preferred embodiment of the present invention, the composition may additionally comprise ascorbic acid (vitamin C), preferably in an amount ranging from about 40-50 mg per 15 mg of elemental iron. The ascorbic acid enhances the absorption of the iron into the bloodstream, providing a more effective composition. Further, the absorption of iron is known to be enhanced in the presence of reducing compounds. Examples of reducing compounds are compounds containing sulfhydryl groups such as the amino acids, lysine and histidine. The absorption of iron is also enhanced in the presence of meat. Accordingly, the present composition can advantageously be consumed with meat. Alternatively, the present composition may additionally contain dessicated meat particles to provide enhanced iron absorption and to provide protein content that would be particularly desirable for administration to populations in which protein consumption is low, such as populations in developing countries.

[0021] Alternatively, or additionally, the present composition may be supplemented with other micronutrients, particularly those micronutrients which are typically absent from the diet or present in insufficient quantities. Examples of micronutrients that may be added to the composition include vitamin A, zinc and iodine, provided in appropriate bioavailable form. In this regard, vitamin A may be added to the present composition in the form of retinyl palmitate, zinc may be added in the form of zinc sulfate or zinc gluconate, while iodine may be added in the form of potassium iodide. It will be appreciated that suitable amounts of additional micronutrients will vary with the micronutrient in question. For example, amounts of about 0.35 - 0.45 mg of retinyl palmitate per 15 mg of elemental iron, about 5-10 mg of elemental zinc per 15 mg of elemental iron and about 0.25 - 0.5 mg of iodine per 15 mg of elemental iron may appropriately be added to the present composition.

[0022] A method useful to prevent iron deficiency anemia in a mammal is also provided. The method involves the steps of adding a therapeutically effective amount of the present composition to a food, and then administering the food to the mammal requiring treatment. The term "therapeutically effective" as it is used with respect to the present composition refers to an amount which is effective to prevent iron deficiency anemia, or at least minimize the occurrence of adverse effects related thereto, while not exceeding an amount which would be toxic or otherwise harmful. In this regard, precise dosage sizes appropriate to prevent anemia can readily be established in appropriately controlled trials. It is anticipated that an effective treatment regimen will be the administration of a dosage in the range of about 10 - 25 mg per day, more preferably about 10 - 17 mg per dey. This dosage is applicable for administration to infants and young children, i.e. children between the ages of 2 - 5 years, as well as being appropriate for administration to older children, i.e. children above 5 years of age, and adults. Administration of larger amounts, for example, 15 - 34 mg per day may be required by pragnant women.

[0023] It will be appreciated that there is no restriction on the foods or beverages to which the present composition can be added. Since the present composition is particularly beneficial for use in the prevention of anemia in infants and young children, the composition will typically be added to foods and beverages generally consumed by infants and young children. Examples of such foods include pureed or semi-solid foods, for example cereals, gruels, porridges, purees of fruit, vegetables, meat or mixtures thereof, as well as milk-based products including, but not strictly limited to, milk, powdered milk, infant formula, puddings, yoghurt, creamed cheese, cottage cheese, and other dairy products which form a part of the diet of infants and young children. The term milk-based products is also meant to include milk substitutes including lactose-free milk and associated products, soy milk and the like.

[0024] In another aspect of the present invention, there is provided an article of manufacture including packaging material and a pharmaceutical composition contained within said packaging material which is therapeutically effective to prevent iron deficiency anemia. The composition comprises a therapeutically effective amount of micro-encapsulated iron granules in combination with a lipid-based excipient. The packaging may indicate that the composition is effective to prevent iron deficiency anemia, or may indicate that the composition contains iron and ingestion of iron prevents anemia. The packaging may further include directions for use, either in written format or in the form of a series of simple illustrations.

[0025] In a preferred embodiment, a single daily dosage of the composition is packaged, for example in a sachet-type package, comprising about 10 -17 mg of elemental iron in the form of micro-encapsulated granules and about 400 - 450 mg of excipient. In a particularly preferred embodiment, the package will additionally include ascorbic acid in an amount of about 40 - 50 mg.

[0026] The present invention is described in more detail by reference to the following specific examples which are not to be construed as limiting.

Example 1 - Preparation of an Iron-containing Composition

[0027] Encapsulated ferous fumarate 60% (1 gram delivers 600 mg ferrous fumarate), having a particle size of no more than about 850 microns in which about 99% of the particles pass through a U.S. No. 20 sieve, was obtained from Watson Foods Co., Inc. (Connecticut).

[0028] Ascorbic acid (3.5 kg; obtained from Basf) was thoroughly mixed in a large aluminum bowl with an excipient

(25 kg; obtained from New Dundee Creamery, Division of Ault Foods Limited) containing corn syrup solids, hydrogenated vegetable oil and/or hydrogenated coconut oil, sodium caseinate, potassium phosphate di-basic, sodium phosphate di-basic, mono and diglycerides, acetylated tarteric acid esters of monoglycerid s, artificial colour, and natural and artificial flavour.

[0029] In a 2-stage fill, 65 mg eliquots of encapsulated ferrous fumarate was added to foil-lined sachet packets followed by the addition of 450-500 mg of ascorbic acid/excipient mixture. The sachets were appropriately sealed along their open edge.

[0030] Optionally, 2.1 kg zinc gluconate is admixed with the ascorbic acid and excipient. This mixture is then added to ferrous fumarate-containing sachets as set out above.

Example 2 - Relative Bioavailability of Micro-encapsuleted Iron

[0031] The bioavailability of iron in the composition set out in Example 1 has been determined using the hemoglobin-repletion test in rats as follows.

[0032] Male weanling Sprague-Dawley rats housed individually in stainless steel cages were fed a low-iron diet and de-ionized distilled water ad lib for 24 days. The low-iron diet contained no more then about 3 mg of iron per kg of diet. Following the 24 day depletion period, approximately 200 µl of blood was drawn from the tail vein of each rat for hemoglobin analysis. Anamic rats having hemoglobin values between 30 and 60 g/L were used in the study. The rats were housed individually in cages in a randomized block design. The rats were divided into groups, each group being fed ad libitum a test diet selected from 0, 10 or 20 mg of one of micro-encapsulated or coated ferrous fumarate (prepared as described in Example 1), micro-encapsulated or coated ferrous fumarate with zinc, uncoated ferrous fumarate particles or uncoated ferrous sulphate (a reference compound determined to have a relative bioavailability of 100) per kilogram of diet. The following chart more specifically sets out the test groups:

# of Animals	Ferrous Sulfate ($FeSO_4.7H_2O$)	Coated Ferrous fumarate	Coated Ferrous fumarate + zinc	Ferrous fumarate
10	0	0	0	0
10	10 mg Fe/kg diet	0	0	0
10	20 mg Fe/kg diet	0	0	0
10	0	10 mg Fe/kg diet	0	0
10	0	20 mg Fe/kg diet	0	0
10	0	0	0 Fe; 10 mg/kg Zn	0
10	0	0	10 Fe; 10 mg/kg Zn	0
10	0	0	20 Fe; 10 mg/kg Zn	0
10	0	0	0	10 mg Fe/kg diet
10	0	0	0	20 mg Fe/kg diet
Total 100				

[0033] The results, as shown in Figure 1, indicate that hemoglobin response is dependent on the amount of iron in the rat's diet. Moreover, there was no significant difference in the hemoglobin response between rats fed similar amounts of iron as the reference compound (ferrous sulfate) versus rats fed micro-encapsulated ferrous fumarate. Referring to Fig.1, the control group represents rats fed a diet containing no iron, the "low iron" diet represents a diet containing 10 mg micro-encapsulated ferrous fumarate/kg of diet, the "high iron control" diet represents a diet containing 20 mg ferrous sulfate/kg of diet and the "high iron" diet represents a diet containing 20 mg micro-encapsulated ferrous fumerate/kg of diet. There was no change in the hemoglobin of the control after 14 days of feeding, while mean hemoglobin response of the low iron diet group was 18 g/L and the mean hemoglobin response of the high iron control and high iron diet groups was 31 g/L and 33 g/L, respectively.

Exemple 3 - Pilot Study to Determine the Efficacy of the Present Iron-containing Composition to Prevent Anemia

[0034] Sixty infants betwean the ages of 6 and 12 months were recruited into the study following parental consent. The hemoglobin of each infant was determined using a fingar prick blood sample. Non-anemic infants were then randomized in a double-blind fashion to receive daily sachets containing e placebo or micro-encapsulated iron composition as prepared in Exampla 1.

[0035] Thirty infants will receive the placebo-sachets for 2 months, and thirty infants will receive the iron-containing sachets for 2 months. At the end ot the two month period, tha hamoglobin ot each intant will be determined by taking a second finger prick blood sample. The difference in the number of anemic infants in each group will be calculated and will indicate the efficacy of the iron-containing composition.

Claims

1. A composition useful to prevent iron deficiency anemia comprising micro-encapsulated iron granules in combination with a pharmaceutically acceptabla lipid-based excipiant.

2. A composition as defined in claim 1, wherein said composition additionally comprises a bio-available form of at least one compound selected from the group consisting of ascorbic ecid, a reducing compound, zinc, vitamin A and iodine.

3. A composition es defined in claim 1, wherein the Iron grenules ere no mora than about 850 microns in diameter.

4. A composition as defined in claim 1, wherein the iron granules are encapsulated with an inert coating, said coating being prepared trom at least one compound salected from tha group consisting of monoglycerides, diglycerides, ethyl callulose, hydrogenated soybean oil and mixtures thereof.

5. A composition as defined in claim 1, wherein said excipient is an edible oil in hydrogenated form.

6. Use of a composition comprising micro-encapsulated iron granules in combination with a pharmaceutically acceptable lipid-based excipient for the manutacture of a medicament to prevent iron deficiency anemia in a mammal.

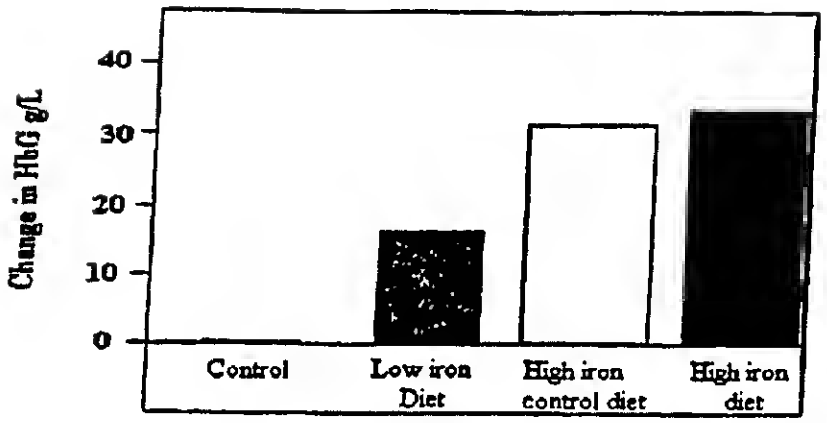
7. Use as defined in claim 6, wherein a therapeutically effective amount of said composition Is added to a food to be administered to said mammal.

8. Use as defined in claim 7, wherein said therapeutically effective emount comprises about 10-25 mg ot elemental iron.

9. Usa as defined in claim 6, wherein the composition additionally comprises at least one compound selected from the group consisting of ascorbic acid, a reducing compound, zinc, vitamin A and iodine.

10. Use as defined in claim 6, wherein the excipient is an edible oil in hydrogenated form.

Figure 1


Change in HbG g/L
40
30
20
10
0
Control
Low iron Diet
High iron control diet
High iron diet

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 99 30 1390

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X Y	WO 97 15201 A (PROCTER & GAMBLE) 1 May 1997 (1997-05-01) * page 3: "SUMMARY OF THE INVENTION" * * page 5-6: "Iron Source" * * page 10: "Clouding/Thickening Agent" * * claims; examples 1,2 *	1-10 1-10	A61K33/26 A61K9/50
Y	WO 93 13783 A (HOLM CHRISTENSEN BOERGE) 22 July 1993 (1993-07-22) * page 5, line 9 - page 7, line 5 * * page 10, line 22 - page 12, line 33 * * page 32, line 23 - page 33, line 2 * * claims 1,23,24; example 1 *	1-10	
X	GB 1 342 974 A (MERCK & CO INC) 10 January 1974 (1974-01-10) * column 1, line 11 - line 45 * * column 2, line 92 - column 3, line 11 * * column 3, line 29 - line 51 * * examples * * claims, especially claims 7-9 *	1,3,4, 6-8	
A	US 3 992 556 A (KOVACS LOUIS E ET AL) 16 November 1976 (1976-11-16) * column 3, line 11 - column 4, line 30 * * column 5, line 48 - column 6, line 16 * * claims; examples *		TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	6 August 1999	Epskamp, S

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 99 30 1390

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

06-08-1999

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9715201 A	01-05-1997	AU 7455996 A	15-05-1997
		BR 9611253 A	30-03-1999
		CN 1202804 A	23-12-1998
		EP 0871378 A	21-10-1998
		PL 326389 A	14-09-1998
		WO 9848648 A	05-11-1998
WO 9313783 A	22-07-1993	AT 153857 T	15-06-1997
		AU 3449193 A	03-08-1993
		CA 2126699 A,C	22-07-1993
		DE 69311306 D	10-07-1997
		DE 69311306 T	29-01-1998
		DK 621784 T	22-12-1997
		EP 0621784 A	02-11-1994
		ES 2105219 T	16-10-1997
		NZ 246866 A	26-07-1995
		US 5662922 A	02-09-1997
		DE 69221166 D	04-09-1997
		DE 69221166 T	05-03-1998
		EP 0641236 A	08-03-1995
		US 5487916 A	30-01-1996
GB 1342974 A	10-01-1974	NONE	
US 3992556 A	16-11-1976	US 3992555 A	16-11-1976

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82